SUPPLEMENTAL FIGURES

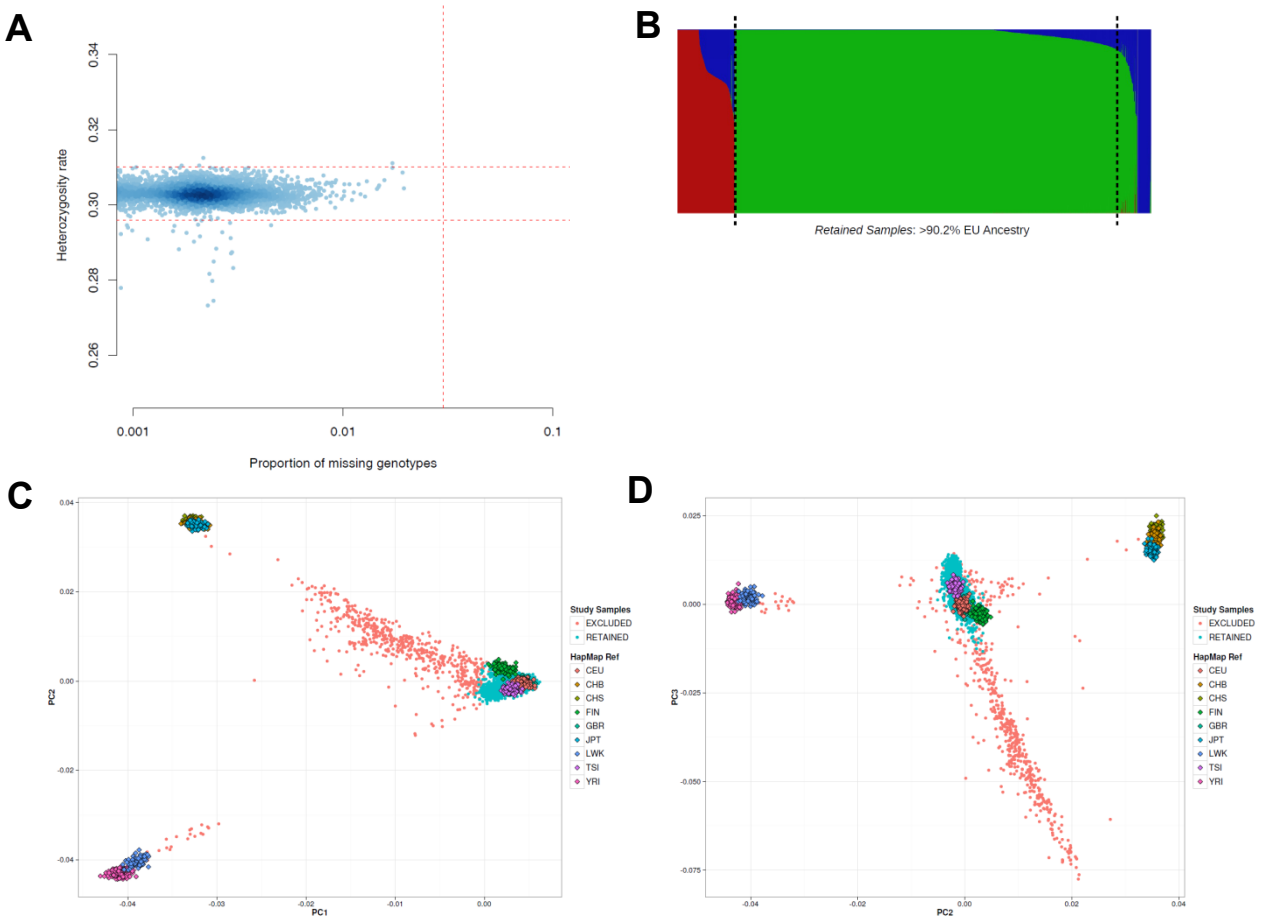


Figure S1. Related to Figure 1. SNP-based quality control and ancestry determination.

(A) Exclusion of sample outliers based on heterozygosity, mean +/- 3 SD (red dotted lines).

(B) Exclusion of non-European samples based on ethnicity estimation using fastStructure with HapMap continental groups and K=3 clustering. Samples with > 9.85% non-EU ancestry were excluded. This threshold was calibrated against the maximum of reference HapMap/1000 Genomes European groups CEU, GBR, and TSI.

The results of principal component (PC) analysis for the cohort and reference groups are plotted along (C) PCs 1 and 2 and (D) PCs 2 and 3. Retained samples and excluded samples are shown in cyan and pink, respectively. CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; CHB, Han Chinese in Beijing, China; CHS, Southern Han Chinese; FIN, Finnish in Finland; GBR, British in England and Scotland; JPT, Japanese in Tokyo, Japan; LWK, Luhya in Webuye, Kenya; TSI, Toscani in Italia; YRI, Yoruba in Ibadan, Nigeria.

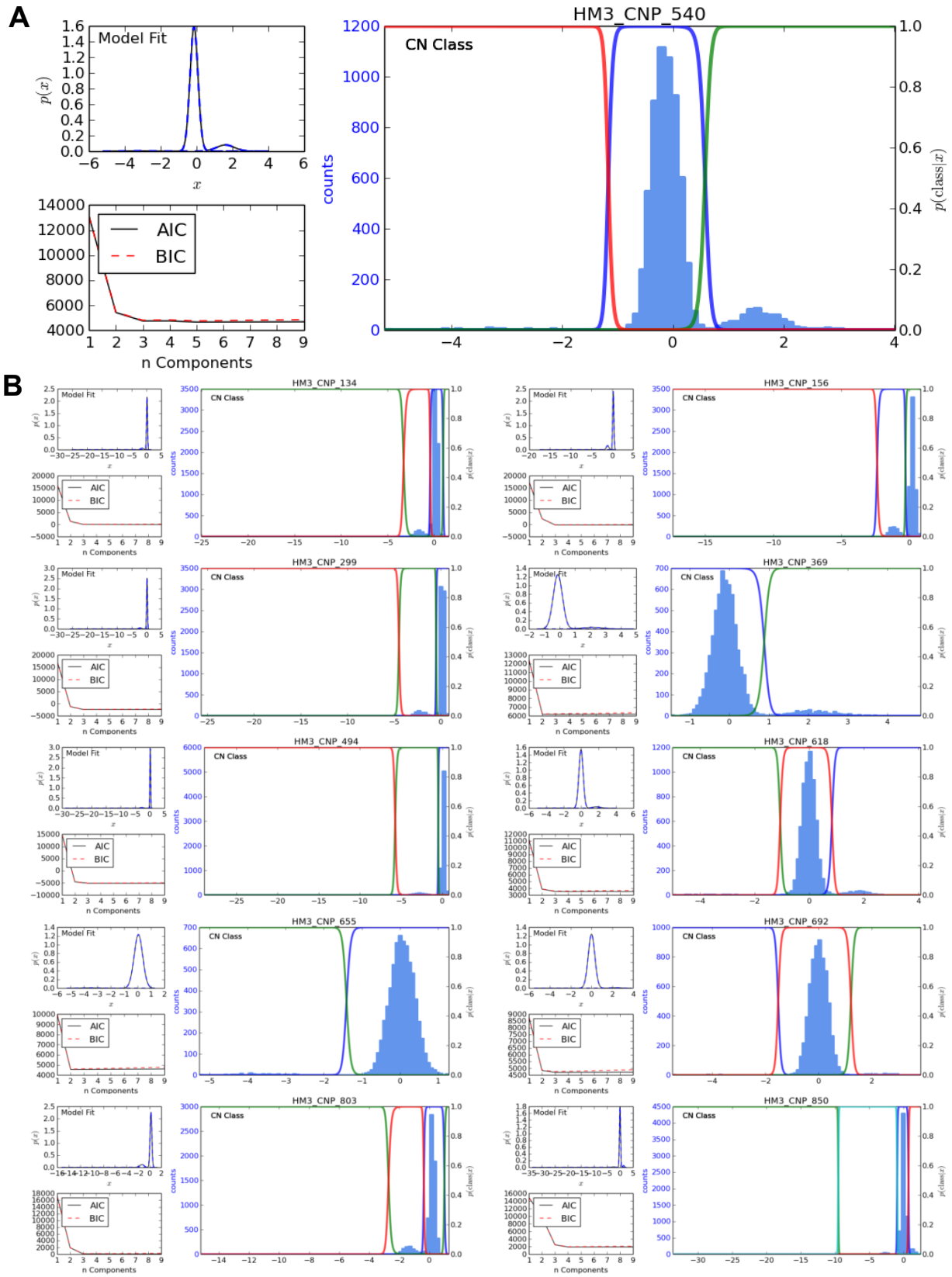

A
Model Fit
p(x)
x
AIC
BIC
n Components
HM3_CNP_540
CN Class
counts
p(class|x)
B
HM3_CNP_134
HM3_CNP_156
HM3_CNP_299
HM3_CNP_369
HM3_CNP_494
HM3_CNP_618
HM3_CNP_655
HM3_CNP_692
HM3_CNP_803
HM3_CNP_850

Figure S2. Related to Figure 1, Tables S2 and S3. **Gaussian mixture model (GMM) clusters of common HapMap3 CNVs.**

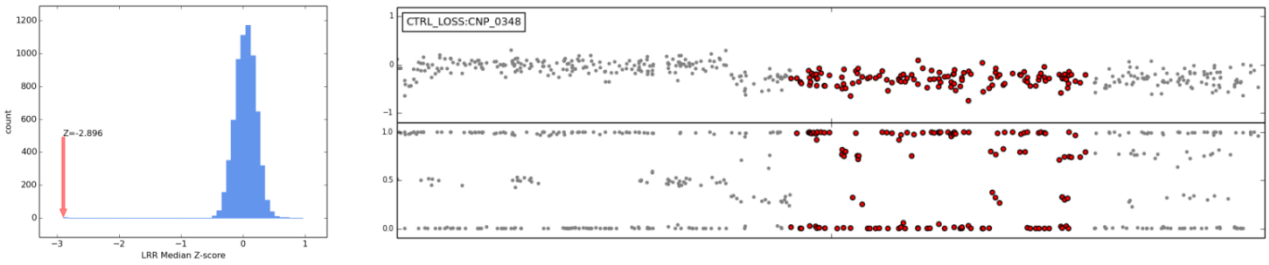
(A) A representative GMM cluster plot for locus HM3_CNP_540. Subplots for each CNV depict, counter-clockwise: the best-fit model, Akaike and Bayesian Information Criterion metrics calculated for GMM fitting 1-9 components, and the posterior probability for CNV cluster assignment (colored lines) overlaying the distribution of median summarized intensity values for all samples across region calculated using the best-fit model.

(B) GMM plots for the 10 additional HapMap3 CNV loci that were used to critically evaluate sensitivity between cases and controls (STAR Methods, Table S2 and S3).

A

SAMPLE_ID	CHR	BP1	BP2	COPY	#SNPS	START_SNP	END_SNP	LRR-Z	BAF_{del}	BAF_{dup}	OUTLIER-Z
CNP_0348	6	67801176	67887156	1	21	rs9363696	rs16899159	-2.96	0.62	0.38	0.00015
CNP_0348[1]	**6**	**67907952**	**68586809**	**1**	**120**	**rs12197620**	**rs9354637**	**-2.90**	**0.76**	**0.16**	**0.00015**
CNP_0348	6	68707131	69142008	1	96	rs4707250	rs9363918	-2.93	0.73	0.17	0.00015
WT_0533[2]	**10**	**47375657**	**47703869**	**3**	**48**	**rs28599894**	**rs4434935**	**2.48**	**0.33**	**0.63**	**0.09**
CC_0852	10	47375657	47703869	3	48	rs28599894	rs4434935	2.36	0.33	0.60	0.09
WT_0866	10	47375657	47703869	3	48	rs28599894	rs4434935	2.33	0.38	0.60	0.09
TS_0457	10	47375657	47703869	3	48	rs28599894	rs4434935	2.29	0.39	0.60	0.09
TS_1843	10	47375657	47703869	3	48	rs28599894	rs4434935	2.05	0.39	0.60	0.09

B



C

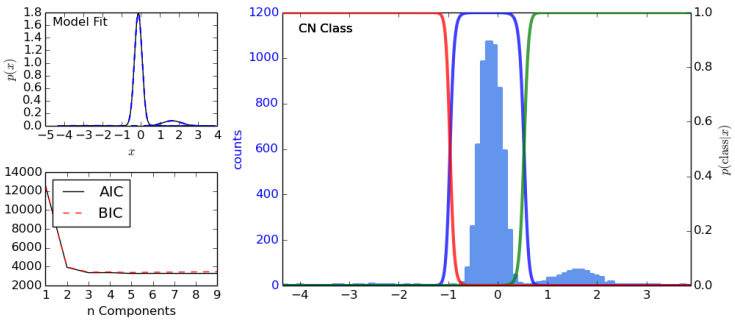


Figure S3. Related to Figure 1. *In silico* validation of CNV calls.

(A) Representative CNVs scored with various CNV validation metrics. Abbreviations (see STAR Methods for details): median summarized intensity measures across a putative CNV locus, standardized by sample (LRR-Z), proportion of probes with a B-Allele Frequency (BAF) banding pattern indicative of a duplication event (BAF-D), proportion of samples with LRR-Z scores indicative of a polymorphic event (OUTLIER-Z).

(B) Example of a large singleton mosaic event flagged for exclusion in sample CNP_0348, indicated as (1) in Figure S3A. This CNV on chromosome 6 was detected as three separate CNVs after taking the consensus of two different HMM calling algorithms. The largest CNV call exhibits an LRR-Z score of -2.86 (left, red arrow), indicative of a deletion, but shows a clear BAF-banding pattern of a duplication event (right), with a BAF_{dup} score of 0.16. This is indicative of a mosaic event, where only a proportion of cells from sample CNP_0348 harbor the deletion event.

(C) Example of a polymorphic CNV on chr10:47,375,657-47,703,869 misclassified as a rare event due to reduced sensitivity, indicated as (2) in Figure S3A, with an OUTLIER-Z score of 0.09. Genotyping by GMM-based clustering (STAR Methods) indicated that this misclassified rare event has a MAF of 0.12.

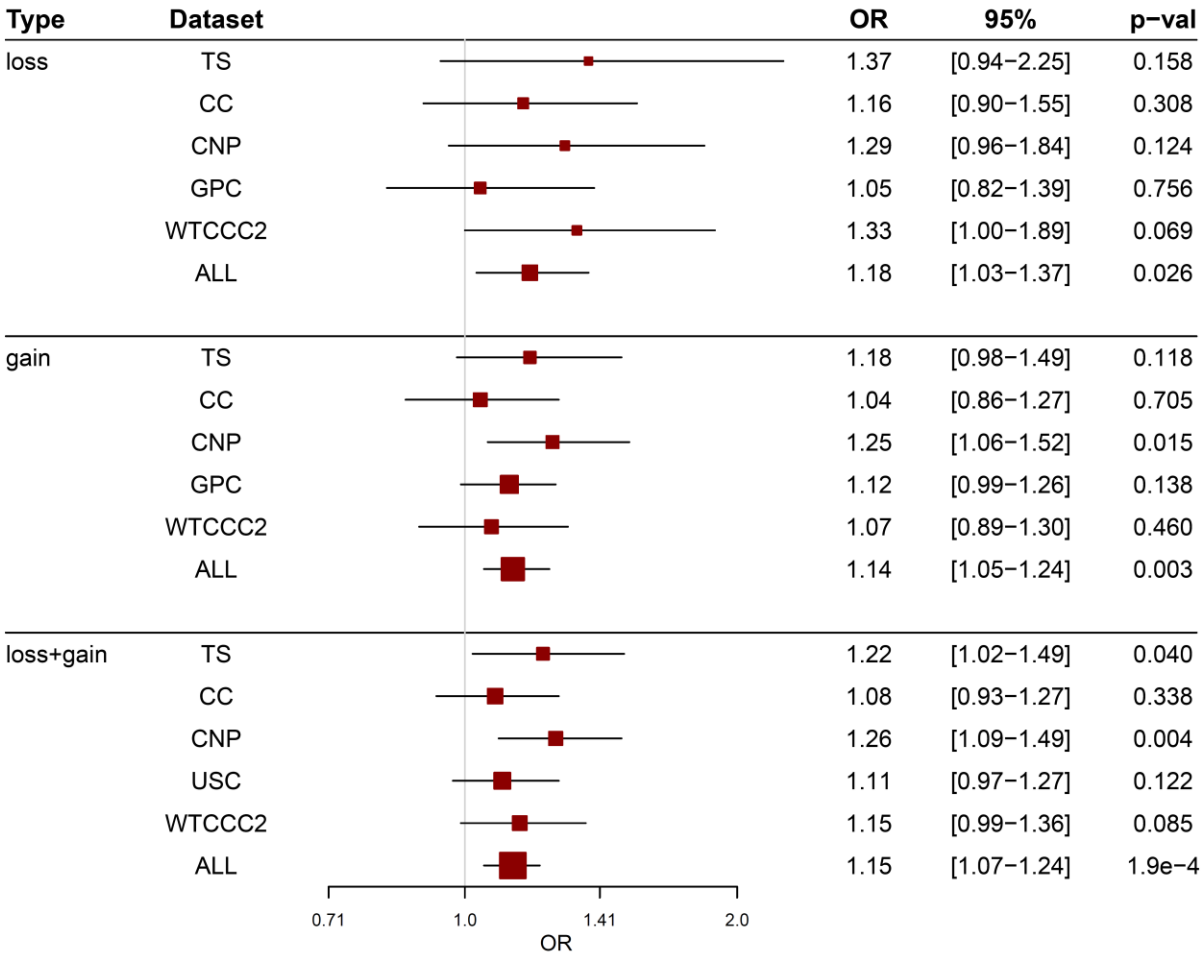
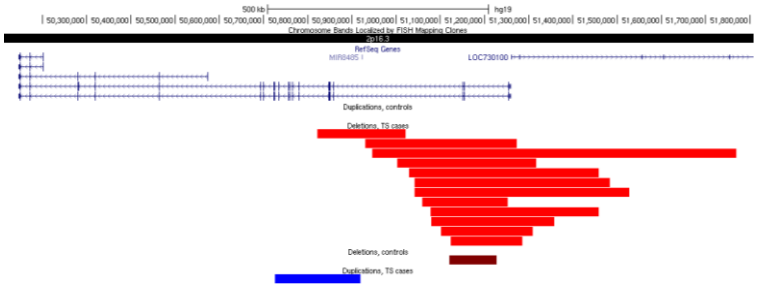
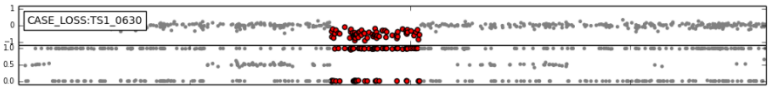
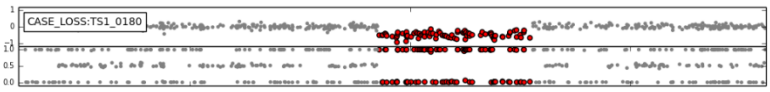


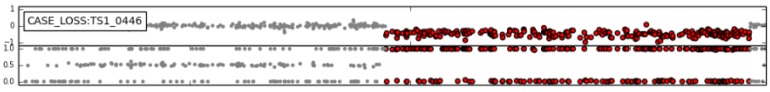
Figure S4. Related to Figure 2. Elevated CNV burden is consistent across datasets.

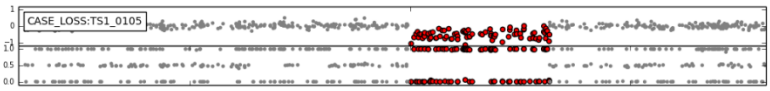
We assessed for increased CNV burden using different metrics and found that total CNV length was most significantly associated with an increased risk for TS (Figure 2). To ensure that the enrichment signal was not driven by a single dataset, here we repeated the assessment of burden by total CNV length, examining all TS samples compared to each of the control sample sets individually and to all control samples together. An increased burden is consistent across all datasets, and additionally when stratified by CNV type: loss (deletions); gain (duplications) and loss + gain (both deletions and duplications). TS, controls collected and genotyped alongside TS cases; CC, CNP, USC, WTCCC2, control samples taken from external datasets (see Table S1A and STAR Methods).

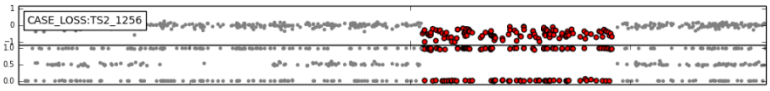

500 kb
hg19
50,300,000 50,400,000 50,500,000 50,600,000 50,700,000 50,800,000 50,900,000 51,000,000 51,100,000 51,200,000 51,300,000 51,400,000 51,500,000 51,600,000 51,700,000 51,800,000
Chromosome Bands Localized by FISH Mapping Clones
20152.3
RefSeq Genes
MIR8485
LOC730100
Duplications, controls
Deletions, TS cases
Deletions, controls
Duplications, TS cases

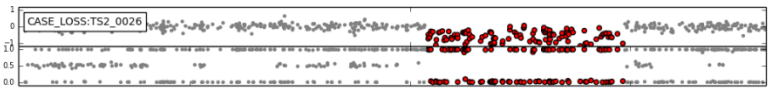

CASE_LOSS:TS1_0630

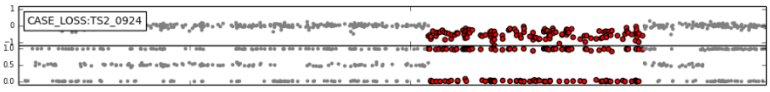

CASE_LOSS:TS1_0180

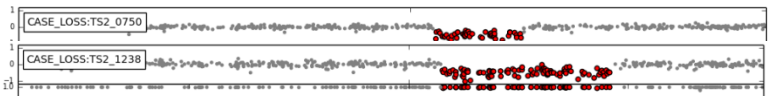

CASE_LOSS:TS1_0446


CASE_LOSS:TS1_0105

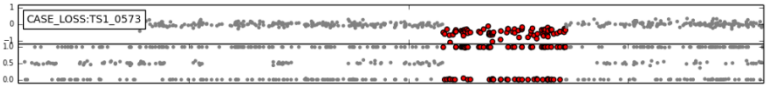

CASE_LOSS:TS2_1256


CASE_LOSS:TS2_0026


CASE_LOSS:TS2_0924


CASE_LOSS:TS2_0750

CASE_LOSS:TS2_1238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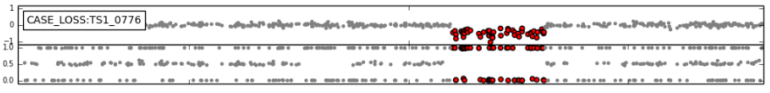
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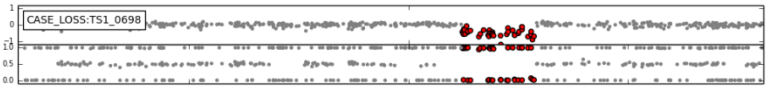
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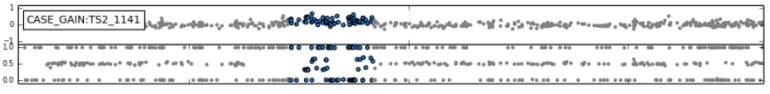
CASE_GAIN:TS2_1141

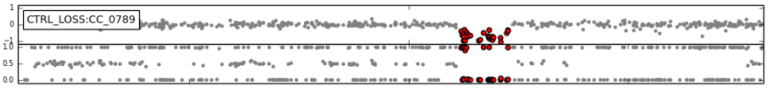
CTRL_LOSS:CC_0789

Figure S5. Related to Figure 4. Exonic CNVs affecting *NRXN1*

UCSC genome browser track depicting all exonic *NRXN1* CNVs > 30kb identified in this study: 12 heterozygous case deletions (red), one control deletion (dark red) and a single case duplication (blue). Probe-level plots of Log-R Ratio (LRR) intensity and B-Allele Frequency (BAF) for all exonic *NRXN1* CNV carriers are shown beneath in the same order as the UCSC genome browser track. Colored probes indicate the location of called deletions (red) and duplications (blue).

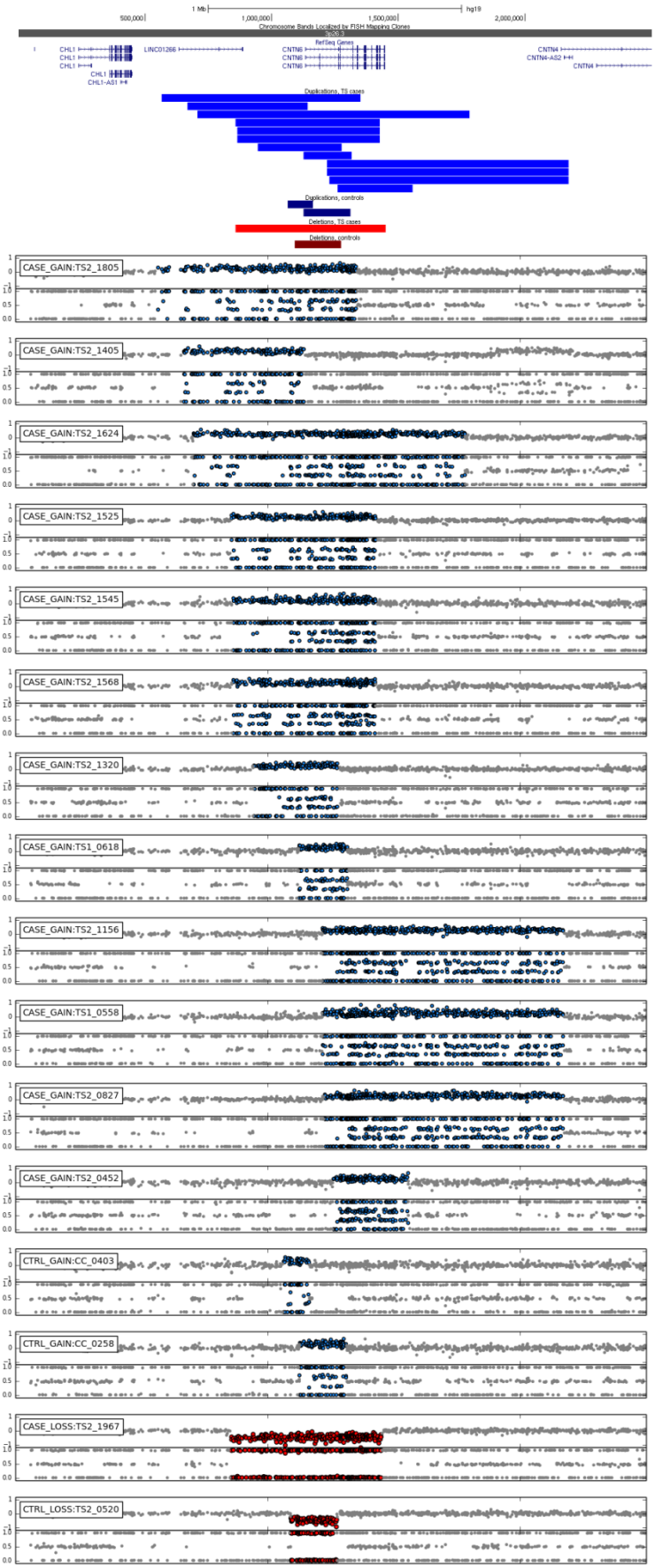
1 Mb
hg19
500,000
1,000,000
1,500,000
2,000,000
Chromosome Bands Localized by FISH Mapping Clones
RefSeq Genes
CHL1
CHL1
CHL1
CHL1
CHL1-AS1
LINC01266
CNTN6
CNTN6
CNTN6
CNTN4
CNTN4-AS2
CNTN4
Duplications, TS cases
Duplications, controls
Deletions, TS cases
Deletions, controls
CASE_GAIN:TS2_1805
CASE_GAIN:TS2_1405
CASE_GAIN:TS2_1624
CASE_GAIN:TS2_1525
CASE_GAIN:TS2_1545
CASE_GAIN:TS2_1568
CASE_GAIN:TS2_1320
CASE_GAIN:TS1_0618
CASE_GAIN:TS2_1156
CASE_GAIN:TS1_0558
CASE_GAIN:TS2_0827
CASE_GAIN:TS2_0452
CTRL_GAIN:CC_0403
CTRL_GAIN:CC_0258
CASE_LOSS:TS2_1967
CTRL_LOSS:TS2_0520

Figure S6. Related to Figure 4. Exonic CNVs overlapping *CNTN6*.

UCSC genome browser track displaying heterozygous genic duplications in TS cases (blue) and controls (dark blue) followed by deletions (red). Probe-level LRR and BAF plots for all 16 CNVs detected spanning *CNTN6* are shown below the genome browser track in the same order. Colored probes indicate the location of called deletions (red) and duplications (blue).

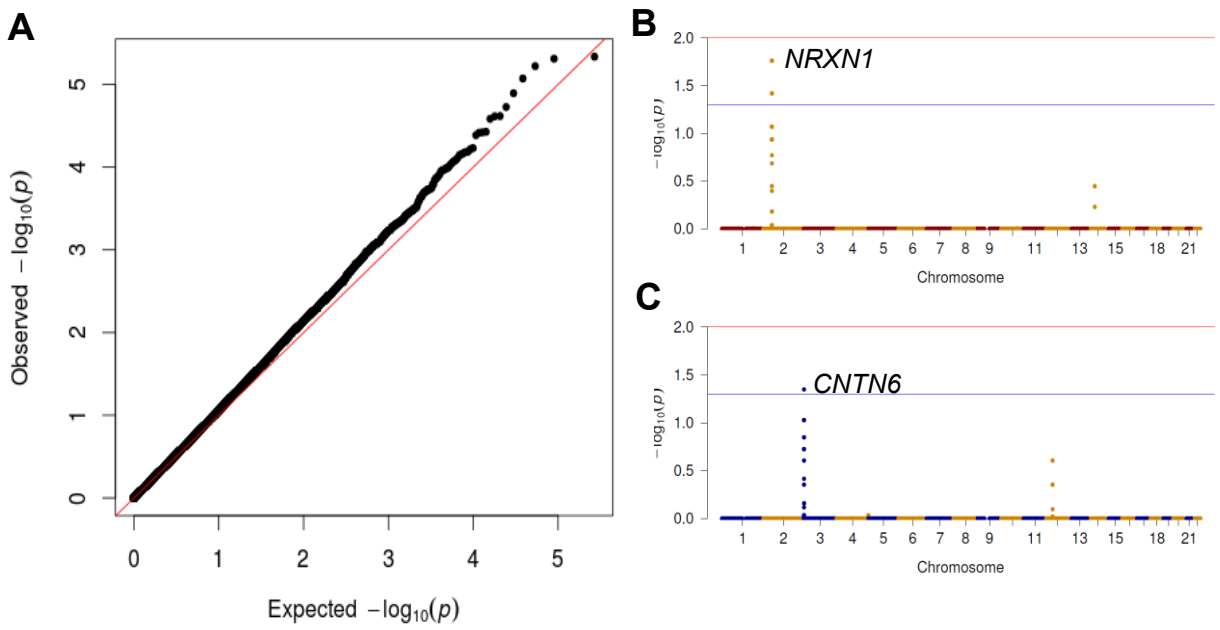

Figure S7. Related to Figure 4. Examination of genome-wide TS case-control CNV analysis for population-specific effects.

To verify the robustness of our results to population stratification, we pair-matched each case subject with exactly one control such that the global difference between all pairs is minimized using Gem Tools (Lee et al., 2010).

(A) The SNP-based λ_{gc} of the resultant dataset (1996 cases and 1996 controls) was an acceptable 1.082. Manhattan plots of segmental association results demonstrate that (B) deletions in *NRXN1* and (C) duplications in *CNTN6* are significant with an $\alpha < 0.05$ (blue line). Deletions and duplications were analyzed separately. The -log10 (p-value) displayed is empirically corrected for FWER (family-wise error rate) genome-wide using the max(T) method with 1,000,000 permutations.

SUPPLEMENTAL TABLES

A. Studies and genotyping			
GENOTYPING BATCH	**ARRAY**	**CENTER**	**PHENOTYPES**
CC	OmniExpress v 1.0	Cardiff	Control
CNP	OmniExpress v 1.0	Broad	Control/Clinical
GPC	OmniExpress v 1.0	Broad	Control/Clinical
WTCCC2	OmniExpress v 1.0	Cardiff	Control
TS1	OmniExpress Exome v 1.1	UCLA	Control/TS
TS2	OmniExpress Exome v 1.1	UCLA	Control/TS
TS3	OmniExpress Exome v 1.1	UCLA	Control/TS

B. QC summary								
QC STEP	**CC**	**CNP**	**GPC**	**WTCCC2**	**TS1**	**TS2**	**TS3**	**TOTALS**
Sample Genotypes	1,146	1,511	3,197	960	1,152	2,160	136	10,262
Pre-cluster QC	1,141	1,510	3,126	870	1,148	2,152	135	10,082
Sex Concordance	1,141	1,510	3,125	870	1,146	2,149	135	10,076
Replicates/Loading Control	1,141	1,491	3,081	870	1,134	2,143	134	9,994
Cryptic Relatedness	1,106	1,430	2,914	855	1,121	2,110	133	9,669
Clinical Phenotype	1,106	1,268	1,342	855	1,121	2,110	133	7,935
EU Ancestry	1,101	646	1,232	842	1,076	2,001	129	7,027
Heterozygosity	1,089	644	1,223	837	1,069	1,986	129	6,977
Intensity QC	1,068	634	1,143	810	959	1,805	116	6,535
CNV Load QC	1,067	634	1,141	808	958	1,803	116	6,527

Table S1. Related to Figure 1. Sample genotyping and QC summary.

(A) Summary of included studies and genotyping information. Sample phenotypes, genotyping platform, and genotyping center for different datasets collected for this study are shown, separated by study.

(B) Summary of quality control procedures by study. The number of samples remaining within each batch after each successive quality control step (see STAR Methods) is shown. Study abbreviations: Cardiff Controls (CC), Consortium for Neuropsychiatric Phenomics (CNP), Genomic Psychiatry Cohort (GPC), Wellcome Trust Case-Control Consortium (WTCCC2) and TS cases and controls collected for this study (TS1-3).

GMM calls at common HapMap3 CNVs								
CNV_ID	CLUSTER	CLUSTER_LRR	GMM_COPY	CTRL_CALLS	CASE_CALLS	CTRL_FREQ	CASE_FREQ	p-value
HM3_CNP_134	1	-13.17478812	0	7	4	0.002	0.002	1.0
HM3_CNP_134	2	-1.544234008	1	296	191	0.072	0.078	0.4
HM3_CNP_156	1	-1.141264855	1	517	315	0.126	0.129	0.7
HM3_CNP_156	2	-10.96495207	0	18	13	0.004	0.005	0.6
HM3_CNP_299	1	-2.148959932	1	275	142	0.067	0.058	0.2
HM3_CNP_299	2	-20.27406193	0	4	3	0.001	0.001	0.7
HM3_CNP_369	1	2.201328191	3	234	137	0.057	0.056	0.9
HM3_CNP_494	1	-2.7402128	1	196	100	0.048	0.041	0.2
HM3_CNP_494	2	-23.74078464	0	1	1	0.000	0.000	1.0
HM3_CNP_540	1	1.648736036	3	392	263	0.096	0.108	0.1
HM3_CNP_540	2	-3.301784945	1	32	17	0.008	0.007	0.8
HM3_CNP_618	1	-3.470922513	1	44	24	0.011	0.010	0.8
HM3_CNP_618	2	1.817743156	3	167	91	0.041	0.037	0.5
HM3_CNP_655	1	-3.645609914	1	45	34	0.011	0.014	0.3
HM3_CNP_692	0	-4.175170396	1	10	11	0.002	0.005	0.2
HM3_CNP_692	2	2.34262532	3	47	32	0.011	0.013	0.6
HM3_CNP_803	1	-10.64502833	0	15	14	0.004	0.006	0.2
HM3_CNP_803	2	-1.347106673	1	417	258	0.102	0.106	0.6
HM3_CNP_850	1	-31.82000658	0	1	1	0.000	0.000	1.0
HM3_CNP_850	2	-2.649145422	1	74	49	0.018	0.020	0.6
HM3_CNP_850	3	1.410233747	3	165	101	0.040	0.041	0.8

Table S2. Related to Figure 1, Figure S2, and Table S3. Gaussian Mixture Model (GMM) clustered genotype calls at common HapMap 3 CNVs.

For sensitivity analysis, all 6,427 samples used in this study were genotyped across 11 common Hapmap3 CNVs using a locus-specific GMM-based clustering method (see STAR Methods). CNV_ID, HapMap3 accession number; CLUSTER_ID, Arbitrary identifier assigned by the clustering algorithm; CLUSTER_LRR, The mean value of all median-summarized standardized intensity values (LRR-Z) for all samples assigned to the cluster; GMM_COPY, Inferred copy-number state. Call frequencies (FREQ) for 4,093 controls (CTRL) and 2,434 TS cases (CASE) reflect the proportion of GMM-based genotype calls with >0.95 posterior probability of cluster assignment (see STAR Methods). There was no significant difference in CNV genotype frequency between phenotypic groups at any of the 21 non-reference genotype calls across all 11 loci (2-sided Fisher's exact test).

A. Sensitivity analysis by locus									
CNV_ID	CNV_TYPE	GMM_TOTAL	GMM_CTRL	GMM_CASE	HMM_CTRL	HMM_CASE	CTRL_SENSE	CASE_SENSE	p-value
HM3_CNP_134	DEL	498	303	195	300	194	0.99	0.995	1.0
HM3_CNP_156	DEL	863	535	328	531	321	0.993	0.979	0.11
HM3_CNP_299	DEL	424	279	145	279	145	1.000	1.000	1.0
HM3_CNP_369	DUP	371	234	137	208	122	0.889	0.891	1.0
HM3_CNP_494	DEL	298	197	101	197	101	1.000	1.000	1.0
HM3_CNP_540	DUP	655	392	263	391	261	0.997	0.992	0.57
HM3_CNP_540	DEL	49	32	17	32	17	1.000	1.000	1.0
HM3_CNP_618	DEL	68	44	24	44	24	1.000	1.000	1.0
HM3_CNP_618	DUP	258	167	91	166	90	0.994	0.989	1.0
HM3_CNP_655	DEL	79	45	34	45	34	1.000	1.000	1.0
HM3_CNP_692	DEL	21	10	11	10	11	1.000	1.000	1.0
HM3_CNP_692	DUP	79	47	32	47	32	1.000	1.000	1.0
HM3_CNP_803	DEL	704	432	272	428	272	0.991	1.000	0.16
HM3_CNP_850	DEL	125	75	50	75	50	1.000	1.000	1.0
HM3_CNP_850	DUP	266	165	101	164	98	0.994	0.970	0.15
B. Overall sensitivity across common CNVs									
CNV_TYPE	GMM_TOTALS	GMM_CTRL	GMM_CASE	HMM_CTRL	HMM_CASE	CTRL_SENSE	CASE_SENSE	p-value	
DEL+DUP	4758	2957	1801	2917	1772	0.986	0.984	0.53	
DEL	3129	1952	1177	1941	1169	0.994	0.993	0.81	
DUP	1629	1005	624	976	603	0.971	0.966	0.65	
C. Group-wise sensitivity analysis across individuals									
CNV_TYPE	CTRL_SENSE	Std. Error	CASE_SENSE	Std. Error	p-value				
DEL+DUP	0.989	0.002	0.983	0.003	0.15				
DEL	0.996	0.001	0.991	0.002	0.14				
DUP	0.973	0.005	0.967	0.007	0.46				

Table S3. Related to Figure 1, Figure S2, and Table S2. Sensitivity analysis of consensus Hidden Markov Modeling (HMM) segmentation calls.

(A) Comparison of CNV detection sensitivity between cases and controls for each locus individually. The sensitivity of HMM calling for each locus was defined as the number of concordant HMM calls divided by the total number of non-reference genotypes determined through GMM-based clustering, a more sensitive, locus specific method (see STAR Methods). GMM genotypes were collapsed into calls of the same class (CNV_TYPE: DEL, all deletions; DUP, all duplications). P-values were calculated using a 2-sided Fisher exact test.

(B) Overall sensitivity across all loci, stratified by CNV_TYPE. P-values were calculated using a 2-sided Fisher's exact test, comparing concordance rates between cases and controls.

(C) Group-wise comparison of sensitivity between cases and controls based on the sensitivity calculated for each individual (see STAR Methods). No significant difference was observed between phenotypic groups whether considering deletions, duplications, or both in concert P-values calculated using a 2-sided Welch's *t*-test, comparing the average sensitivity by individual between phenotypic groups.

Sample ID	Gene	Chr	Start	End	Type	Length (kb)	Variant Effect	OCD	ADHD	Atypical	Notes
TS1_0630	NRXN1	2	50821559	51021488	DEL	199.9	CODING	N	N	Y	Unspecified Developmental Delay (ICD-9: 315.9)
TS1_0180	NRXN1	2	50930181	51272375	DEL	342.2	CODING	N	N	Y	Asperger Syndrome
TS1_0446	NRXN1	2	50945471	51770480	DEL	825	CODING	Y	Y	N	
TS1_0105	NRXN1	2	51002606	51316822	DEL	314.2	CODING	N	Y	N	
TS2_1256	NRXN1	2	51028662	51458570	DEL	429.9	CODING	N	Y	Y	Other developmental speech or language disorder (ICD-9: 315.39)
TS2_0026	NRXN1	2	51041472	51483528	DEL	442.1	CODING	N	N	N	
TS2_0924	NRXN1	2	51041603	51528298	DEL	486.7	CODING	N	Y	N	
TS2_0750	NRXN1	2	51058745	51252137	DEL	193.4	CODING	Y	Y	Y	Asperger Syndrome
TS2_1238	NRXN1	2	51077569	51458570	DEL	381	CODING	Y	N	Y	Paranoid personality disorder
TS1_0573	NRXN1	2	51079482	51357902	DEL	278.4	CODING	NA	NA	NA	
TS1_0776	NRXN1	2	51101583	51308895	DEL	207.3	CODING	N	Y	N	Brother with Asperger Syndrome
TS1_0698	NRXN1	2	51123048	51286169	DEL	163.1	CODING	Y	Y	N	
TS2_1805	CNTN6	3	565961	1350458	DUP	784.5	CODING	Y	NA	N	
TS2_1405	CNTN6	3	668832	1143424	DUP	474.6	5' UTR	Y	Y	N	
TS2_1624	CNTN6	3	707257	1781739	DUP	1074	CODING	N	N	N	
TS2_1525	CNTN6	3	857325	1427769	DUP	570.4	CODING	Y	Y	N	
TS2_1568	CNTN6	3	864513	1425997	DUP	561.5	CODING	Y	Y	N	
TS2_1545	CNTN6	3	864513	1427769	DUP	563.3	CODING	N	Y	N	
TS2_1320	CNTN6	3	946290	1276092	DUP	329.8	CODING	Y	N	N	
TS1_0618	CNTN6	3	1125605	1315900	DUP	190.3	CODING	N	N	N	
TS2_1156	CNTN6	3	1218279	2170519	DUP	952.2	CODING	N	Y	N	
TS1_0558	CNTN6	3	1218279	2170519	DUP	952.2	CODING	N	Y	N	
TS2_0827	CNTN6	3	1226953	2170519	DUP	943.6	CODING	N	N	N	
TS2_0452	CNTN6	3	1260932	1556680	DUP	295.7	CODING	N	N	N	

Table S5. Related to Figure 4. Clinical phenotypes of *NRXN1* and *CNTN6* CNV carriers.

Clinical phenotypes for all CNV carriers of the two significant TS loci detected in this study: deletions at *NRXN1* and duplications at *CNTN6*. Genomic location is given in hg19 coordinates. For each CNV carrier, the presence of common comorbid disorders for TS, attention deficit disorder (ADHD) and obsessive-compulsive disorder (OCD) is indicated, and atypical diagnoses are flagged and described (Notes). NA, No clinical information available.

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